REMARKS

Applicant respectfully requests reconsideration. Claims 1-6, 9-16, and 49 were previously pending in this application. By this amendment, Applicant is canceling claim 49 without prejudice or disclaimer. New claim 72 has been added. Support for claim 72 can be found throughout the specification as filed, for example, in the paragraph starting on page 13, line 17. As a result, claims 1-6, 9-16, and 72 are pending for examination with claims 1 and 14 being independent claims. No new matter has been added.

Election/Restriction

The Examiner has stated that "[a]s noted by Applicant, claims 1 to 6, 9 to 16 and 49 *read on the elected species*." Office Action at 2, emphasis added. Applicant respectfully disagrees with this characterization of Applicant's statement. Applicant has stated in the reply filed on June 2, 2011, that "[c]laims 1-6, 9-16, and 49 *are believed to represent a grouping representative of the elected invention*" (emphasis added).

Application Data Sheet

The Examiner has noted that the citizenship of inventor Adra is not consistent between the oath and the Application Data Sheet. Office Action at 4.

Applicant submits that the citizenship of inventor Adra is correctly set forth on the oath. A corrected Application Data Sheet is filed together with this response.

Rejections under 35 U.S.C. §112

Claims 1-6 and 9-16 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, while being enabling for a method of detecting statistically significant differences in the mRNA expression pattern observed between normal, healthy

mammalian subjects and mammalian subjects known to possess a granulocyte disorder and a method for detecting the presence of chronic myelogenous leukemia in human subjects based on differential expression of a plurality of genes, including HTm4, in bone marrow samples as described by Nowicki, does not reasonably provide enablement for detecting the presence of any granulocyte disorder in any biological sample obtained from any subject based solely on an observed statistically significant difference in the expression level of the HTm4 gene." Office Action at 5.

In her reasoning to support the rejection, the Examiner has stated that "the working examples do not demonstrate an association between altered HTm4 expression and even one of the many granulocyte disorders encompassed by the claims." Page 5 of the Office Action. Regarding the state of the prior art and unpredictability in the art, the Examiner has stated that "Erle cautions that asthma is a very complicated disorder and that further validation of the results obtained from microarray analysis of mRNA expression patterns is required before observed gene expression differences between a normal and asthmatic subject can be used as a stand-alone method of detecting the presence of the disorder in subjects of unknown disease status." Page 6 of the Office Action. The Examiner has also stated that "Erle also teaches that this process is likely 'challenging', due to the complexity of the disease, the need to obtain results from a large number of individuals in a well-designed cohort, and 'the difficulties inherent in obtaining suitable tissue for study'."

The Examiner has further stated that "Nowicki teaches that further validation of the observed chronic myelogenous leukemia mRNA expression signature is needed before the results can be used in a stand-alone assay for detection of the presence of disease in human subjects of unknown disease status [...]." Page 6 of the Office Action.

Applicant disagrees with the Examiner's characterization of the cited art. Neither Erle nor Nowicki teach that the described gene expression signatures could not be used as stand-alone assays for the detection of disease. Both references are, in fact, silent as to the prospect of translating the respective microarray expression signatures into the clinic as diagnostic assays. The cited references are concerned with the use of microarray technology to elucidate the underlying biology

of asthma (Erle) and chronic myelogenous leukemia (Nowicki), but not with the development of diagnostic assays.

Applicant further submits that the Examiner has broadly referred to long passages in the referenced articles (e.g., pages 1-2 of Erle, pages 2-3 of Erle, page 3961 of Nowicki), but not to specific statements, in support of her allegations. Office Action at pages 6 and 7. Since no specific statements were referenced by the Examiner, Applicant has made a good-faith effort to identify any statements that might lend support to the Examiner's position.

The only statement Applicant could identify in the Erle reference is that "asthma microarray studies will be challenging because of the requirement for recruiting a large, clinically well-characterized cohorts of subjects, and the difficulties inherent in obtaining suitable tissue for study. Last paragraph on page 232. This statement refers to the microarray studies themselves, and not, as alleged by the Examiner on page 6, lines 11-18 of the Office Action, to the "process" of "further validation of the results obtained from microarray analysis" towards a "stand-alone" diagnostic method. The Erle reference is silent as to the translation of asthma microarray data into clinical diagnostics, and the above statement refers merely to the challenges in carrying out asthma microarray analyses in order to understand the biology of the disease.

Similarly, Nowicki does not state, as alleged by the Examiner, that "further validation of the observed CML expression signature is needed before the results can be used in a stand-alone assay." Applicant has made a good-faith effort to identify such a teaching on page 3961, as referenced by the Examiner, but could not find any such teaching. The referenced page contains a statement that "caution should be applied because of the differences in composition of the mononuclear cell populations in normal and CML samples." First full paragraph of page 3961. However, the reference also states in the next sentence that "these variations seem not to be a major factor, because the validation tests showed that expression of the reference genes detected by the microarrays was in accordance with the published findings." *Id.* Applicant submits that, first, this statement does not relate to the use of microarrays as diagnostic tools, and second, that this statement does not teach that microarray results have to be further validated. To the contrary, the statement supports a teaching that validation has already been achieved.

Applicant respectfully submits that the Examiner has failed to support her allegations of teachings regarding the use of gene expression methodology in the detection of disease with actual statements in the cited references. Further, Applicant is not aware of any requirement in patent law that a diagnostic method must be able to be used as a stand-alone assay for the diagnosis of a specific disease in order to satisfy the enablement requirement.

The Examiner has also stated that "the prior art, [...] does not teach an association between HTm4 expression levels and a granulocyte disorder." Office Action at page 7. Applicant disagrees and respectfully submits that the instant specification provides, among other embodiments, granulocyte-selective markers, including HTm4, and methods of using these granulocyte-selective markers to detect the presence or absence of a granulocyte disorder in a subject. The instant specification teaches, for example, that the detection of an aberrant level of expression of one or more granulocyte-selective markers, *e.g.*, of HTm4, in a sample obtained from a subject is indicative of the presence of a granulocyte disorder in the subject. Methods of detecting expression levels of granulocyte-selective markers are provided in the specification and additional suitable methods were known in the art. As admitted by the Examiner, the level of skill in the pertinent art was high at the time of filing. Applicant submits that based on the teachings of the instant application, and most prominently the identification of granulocyte-selective markers and related methods, and based on the high level of skill in the art, the skilled artisan was able to detect aberrant expression levels of granulocyte-selective markers in a sample from a subject, merely by comparing the expression level found in that subject to a reference level, for example, a normal level of expression (see, e.g., page 14, last paragraph of the application as filed).

Based on the granulocyte-selective character of the marker genes provided by the instant application, including HTm4, an abnormal level of expression of such a marker in a sample can be due to an abnormal number of granulocytes in the sample, or an abnormal expression level of the marker gene in the granulocytes in the sample, and both situations are defined as a "granulocyte disorder" according to the instant specification (see, e.g., page 3, last full paragraph of the application as filed). Applicant submits that based on the teachings of the instant specification at the time of the filing of the application, the skilled artisan was able to determine whether or not expression of an instantly identified granulocyte-selective marker was at an aberrant level in a

sample from a subject, and also to determine whether or not a granulocyte disorder, e.g., an aberrant high or low number of granulocytes, was present or absent in the subject as a result of such determination according to aspects of the instantly claimed invention.

In summary, Applicant submits that the Examiner has failed to support the alleged "negative teachings in the art" (page 9 of the Office Action) with actual evidence or actual statements found in the cited art, that there is no requirement in patent law that a diagnostic method has to work as a stand-alone assay for diagnosing a specific disease, and that in view of the high skill in the art, the guidance provided in the specification is sufficient for the skilled artisan to practice the invention to the full scope of the currently pending claims without undue experimentation.

Accordingly, withdrawal of the rejection of claims 1-6 and 9-16 under 35 U.S.C. §112 is respectfully requested.

Claims 1-6, 9-16, and 49 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, because, according to the Examiner, "the recitation of GenBank accession numbers, for example, L35848, in independent claims 1, 14, and 49 causes the scope of the claims to be entirely unclear." Office Action at 6. Citing Benson *et al.*, the Examiner has taken the position that nucleic acid sequence records in GenBank are dynamic and may change over time, resulting in the scope of the claims changing over time." *Id.*

Applicant respectfully disagrees. The cited reference, Benson, does not support a finding of indefiniteness for claims citing GenBank accession numbers. To the contrary, the Benson reference supports an argument that the skilled artisan is able to determine the metes and bounds of a GenBank accession number, even though the database is frequently updated, based on GenBank's version-tracking features. Benson states in the section beginning with the first full paragraph of the right column on page D29 (emphasis added):

> **Sequence identifiers and accession numbers**
>
> Each GenBank record, consisting of both a sequence and its annotations, is assigned a unique identifier called an accession number that is shared across the three collaborating databases (GenBank, DDBJ and EMBL). The accession number appears on the ACCESSION line of a

> GenBank record and remains constant over the lifetime of the record, even when there is a change to the sequence or annotation. Changes to the sequence data itself are tracked by an integer extension of the accession number, and this Accession.version identifier appears on the VERSION line of the GenBank flat file. The initial version of a sequence has the extension '.1'. In addition, each version of the DNA sequence is also assigned a unique NCBI identifier called a GI number that also appears on the VERSION line following the Accession.version:
>
> ACCESSION AF000001
> VERSION AF000001.1 GI: 987654321
>
> When a change is made to a sequence in a GenBank record, a new GI number is issued to the updated sequence and the version extension of the Accession.version identifier is incremented. The accession number for the record as a whole remains unchanged, and will always retrieve the most recent version of the record; the older versions remain available under the old Accession.version identifiers and their original GI numbers. A similar system tracks changes in the corresponding protein translations. These identifiers appear as qualifiers for CDS features in the FEATURES portion of a GenBank entry, e.g. /protein_id='AAA00001.1'. Protein sequence translations also receive their own unique GI number, which appears as a second qualifier on the CDS feature:
>
> /db_xref='GI: 1233445'

As noted in Benson, the database entry of a GenBank accession number, such as, for example, L35848, will list the current version of the entry and any prior versions. This version tracking by GenBank allows the skilled artisan to determine which sequence was current at any point in time, *e.g.*, at the time of filing of the instant application. Accordingly, the skilled artisan is able to determine the metes and bounds of a given GenBank accession number within a given time frame. The Benson reference, thus, supports an argument that the recitation of GenBank accession numbers is not indefinite.

Accordingly, withdrawal of the rejection of claims 1-6, 9-16, and 49 under 35 U.S.C. §112 is respectfully requested.

Rejections Under 35 U.S.C. §102

Claims 1, 2, 4, 5, 10, 11, and 13-16 are rejected under 35 U.S.C. §102(a) as being unpatentable over Nowicki et al. (Oncogene (June 203) 22: 3952-3963; cited previously) as

evidenced by Ishibashi et al. (Gene (2001) 264: 87-93; newly cited). Office Action at 8. The Office Action states that "Nowicki teaches a method for detecting the presence of a granulocyte disorder, specifically chronic myelogenous leukemia, by measuring the mRNA expression level of MS4A3 via array hybridization, which, as evidenced by Ishibashi at page 88, column 2, is synonymous with HTm4 [...]." *Id.*

Applicant respectfully disagrees. Nowicki reports findings based on a comparison of gene expression profiles from subjects known to have chronic myelogenous leukemia (CML) to data from healthy individuals. The reference does not teach, however, that the expression data reported would be indicative of or could in any way be used to diagnose CML, or any granulocyte disorder for that matter, in a subject. The reference does not teach that aberrant expression of HTm4, or any of the numerous genes identified to be differentially expressed in CML, could be used as a biomarker indicating a granulocyte disorder, e.g., CML, in a subject. The reference also lacks any teaching of any of the genes identified being a granulocyte-selective gene. Nowicki further does not teach that the genes identified as differentially regulated in CML could be used to predict CML in a subject of unknown disease status. Accordingly, the teachings of Nowicki are neither sufficient to diagnose CML in a subject, nor do they enable one of skill in the art to identify a granulocyte-selective biomarker, e.g., a granulocyte-selective gene as provided by the instant disclosure.

Accordingly, withdrawal of this rejection is respectfully requested.

Claim 49 is rejected under 35 U.S.C. 102(b) as being anticipated by Tedder et al. (WO 2002/062946 A2; newly cited).

Without conceding the correctness of the Examiner's position, and without prejudice or disclaimer, claim 49 has been canceled by this amendment, rendering the rejection moot.

Rejections Under 35 U.S.C. §103

Claim 6 is rejected under 35 U.S.C. §103(a) as being unpatentable over Nowicki et al. as evidenced by Ishibashi et al. in view of Rajeevan et al. (Journal of Molecular diagnosis (2001) 3(1): 26-31; newly cited) and further in view of Adra et al. (Proceedings of the National Academy of Sciences (1994) 91:10178-10182; cited on the IDS).

The deficiencies in the teachings of Nowicki are discussed in more detail above. Briefly, Nowicki does not teach that HTm4 is a granulocyte-selective marker, or that aberrant expression of HTm4 could be used as a biomarker indicating a granulocyte disorder, *e.g.*, CML, in a subject. According to the Examiner, Ishibashi teaches that the designation MS4A3 as used in Nowicki, is synonymous with HTm4. Office Action at page 10. The Rajeevan reference, according to the Examiner, "teaches that RT-PCR should be used to validate the results of array hybridization studies," and the Adra reference evidences that "the sequence of the HTm4 gene was known in the art at the time of the invention." Office Action at page 12.

Without conceding the correctness of the Examiner's characterization of the cited references, the alleged teachings provided by them do not cure the deficiencies of the Nowicki et al. reference. The references, alone or in combination, thus, do not provide that aberrant expression of HTm4 could be used as a biomarker indicating a granulocyte disorder in a subject.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. A0852.70000US01 .

Dated: April 30, 2012

Respectfully submitted,

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